Mucinous Tubular and Spindle Cell Carcinoma of Kidney Occurring in a Patient with Pulmonary Adenocarcinoma

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CASE REPORT

Clinical summary

A 72-year-old man presented with a month-long history of coughing productive of blood-tinged sputum. The patient had no other significant past medical history. A computerized tomographic (CT) examination of the chest showed a spiculated nodule in the left upper lobe of the lung. A diagnosis of pulmonary cancer was suspected, and a metastatic survey was performed, which revealed no evidence of metastatic disease in the brain or bone. However, abdominal CT showed an exophytic right renal mass, which was clinically interpreted to be a metastatic lesion (Fig. 1A). A transbronchial biopsy was performed, resulting in a diagnosis of adenocarcinoma of the lung. A subsequent left upper lobectomy confirmed the biopsy results. The patient then received a combined chemotherapy regimen consisting of 4 cycles of Padexol and carboplatin. Despite chemotherapy, no remarkable change was noted in the renal mass after 6 months, and a
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radical nephrectomy was undertaken due to the possibility of primary renal cell carcinoma. The patient is alive and well 3 months after nephrectomy.

Fig. 1. Computerized tomography of abdomen, and cut surface photograph of renal mass. (A) An exophytic renal mass was noted in the lower pole of the right kidney. (B) The tumor is well circumscribed and the cut surface is solid with multi-nodular configuration.

Fig. 2. Photomicroscopes of kidney tumor and metastatic lesion. (A) Most tumor cells show a predominant pattern of regular spindle cells arranged in sheets resembling sarcoma. (B) Foci of cuboidal cell proliferation, forming cords and tubules are also seen, and the tubules are separated by pale mucinous stroma. (C) Metastatic focus in a hilar lymph node is observed. (D) Alcian blue staining (pH 2.0) reveals the presence of extracellular mucinous material.
Pathologic findings

Gross findings
Examination of the nephrectomy specimen revealed a 5.5 × 4.0 × 3.5 cm cortical mass, located in the inferior pole of the right kidney. It protruded into, but did not invade, the extrarenal adipose tissue (Fig. 1B). The tumor was well-circumscribed, but not encapsulated. The cut surface of the tumor was pale-yellow with a multi-nodular configuration and solid consistency. No hemorrhage or necrosis was found. The left upper lobectomy

Fig. 3. Representative immunohistochemical staining results. The tumor cells show strong reactivity to (A) epithelial membrane antigen, (B) vimentin, (C) renal cell carcinoma antigen, and (D) racemase, (E) p53 and (F) Ki-67.
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specimen from the lung demonstrated a firm mass, measuring 3.5 × 3.0 × 2.5 cm. Areas of hemorrhage and necrosis were seen. Microscopically, the tumor showed a moderately differentiated adenocarcinoma. Peribronchial lymph nodes (20) and mediastinal lymph nodes (2) showed two foci of metastasis: one in each of the peribronchial lymph nodes and mediastinal lymph nodes.

**Microscopic findings**

On microscopic examination of the kidney tumor, the predominant pattern was a spindle cell proliferation, arranged in fascicles (Fig. 2A). Additionally, small foci of epithelial cells forming cords and tubules were recognized (Fig. 2B). In these areas, elongated tubules were separated by pale mucinous stroma, and the tubules were composed of small cuboidal cells with eosinophilic cytoplasm. The nuclei of the tumor cells were small, round, and centrally located, without prominent nucleoli. There was no significant atypia. Mitoses and vascular invasion were not observed. Metastasis to one hilar lymph node (1/1) was noted (Fig. 2C).

To exclude the possibility of metastatic carcinoma to the kidney originating from the lung, the lobectomy specimen was also reviewed. Microscopically, the lung cancer showed moderately differentiated, gland-forming adenocarcinoma without spindle cell areas. The tumor exhibited invasion into the visceral pleura and had one satellite tumor nodule. Metastases were found in two regional lymph nodes (LN#4L). Therefore, pathological stage of the lung cancer was categorized as T4N2. There was no significant atypia. Mitoses and vascular invasion were not observed. Metastasis to one hilar lymph node (1/1) was noted (Fig. 2C).

**Histochemical and immunohistochemical findings**

Alcian blue staining (pH 2.0) of the kidney tumor revealed the presence of extracellular mucinous material in the tubular areas, but not in the spindle cell areas (Fig. 2D).

The tumor cells of MTSCC showed strong, diffuse staining for vimentin, epithelial membrane antigen, renal cell carcinoma antigen, and racemase (AMACR) (Fig. 3). Staining with cytokeratin (CK) 7, prostate specific membrane antigen (PSMA), high-molecular-weight CK (34βE12), and low-molecular-weight CK (35βH11) revealed focal expression of moderate intensity. Additionally, neuron-specific enolase (NSE), chromogranin, synaptophysin, and CD56 were weakly and focally expressed. p53 was strongly expressed in 5% (Fig. 3E), and Ki-67 was expressed in 20% (Fig. 3F). The tumor cells were completely negative for pan CK (AE1/AE3), CK 18, CK 19, CD10, CD15, C-kit, villin, and thyroid transcription factor 1 (TTF-1). The tumor cells in the lymph node were immunohistochemically identical to those seen in the kidney tumor and were negative for TTF-1. In contrast, the lung tumor cells were strongly positive for TTF-1.

**DISCUSSION**

The recent WHO classification system has recognized MTSCC as a distinct entity of renal cell carcinoma, exhibiting a mixed pattern of tubules and a surrounding spindle cell proliferation within a myxoid stroma, showing low-grade nuclear features. Reported cases have shown a female predominance and benign clinical outcome. MTSCC can easily be diagnosed by histology alone, because of its characteristic histologic appearance. However, morphologic diversity of MTSCC has been reported and may create diagnostic difficulty when the histological features are not typical. In the present case, there were some unusual histological features. For example, extracellular mucin and the classic well-defined tubular architecture were noted only focally. Thus, our case was a diagnostic challenge, as the dominant spindle cell component resembled sarcomatoid renal cell carcinoma or a mesenchymal tumor of the kidney. If the tumor had not been sampled adequately, the small foci of tubular architecture may have been overlooked, leading to misdiagnosis. Therefore, it is important that careful microscopic examination of multiple representative sections be performed to identify features of a less common lesion like MTSCC.

The cell lineage and origin of MTSCC still remains undetermined. Initially, Parwani et al. suggested that the morphologic and ultrastructural configuration of MTSCC is similar to the normal loop of Henle, and therefore believed that it originated from the distal nephron. On the other hand, Sun et al. showed CD15 positivity and ultrastructural findings of mitochondria and glycogen, favoring proximal tubule differentiation. Shen et al. also support the belief that this tumor most likely originates from the proximal tubules and suggested that it actually represents papillary renal cell carcinoma with spindle cell features. On immunohistochemistry in our case, the tumor was positive for markers of the proximal tubules (AMACR) as well as for markers of the distal nephron (EMA and CK7). Therefore, the line of differentiation of MTSCC remains unclear because of variability of immunohistochemical results and electron microscopic features. Further studies may help to more accurately determine the origin of this rare tumor.

Interestingly, the tumor cells were immunohistochemically positive for endocrine markers such as NSE, chromogranin, synap-
trophysin, and CD56 in our case. Jung et al. also reported that some MTSCC cases have shown positivity for endocrine markers. So neuroendocrine differentiation should be noted as another immunohistochemical feature in the spectrum of MTSCC. Previous electron microscopy studies have also revealed that these tumors contain cytoplasmic neurosecretory granules.

To date, fewer than 100 cases of MTSCC have been reported. Metastasis was identified in only 2 of these cases, with only regional lymph node metastasis and no distant metastasis. We report an additional case of metastatic MTSCC to a regional lymph node. In our case, the percentage of p53 positive cells was above 5% with strong intensity, which is different from other reported non-metastatic cases and may suggest an association between p53 activity and metastasis in MTSCC. Blandamura et al. found that p53 positivity had a significant correlation with metastasis in clear cell renal cell carcinoma (CCRCC). Pinto et al. also suggested that p53 overexpression correlates with lower disease-related survival in CCRCC. Since the two previously reported metastatic MTSCC cases were not stained with p53, the importance of positivity of p53 and regional lymph node metastasis with respect to clinical outcome is unclear. However, the fact that many cases that showed negative staining of p53 exhibited no metastasis may support the possibility of the positive p53 staining and metastasis. Furthermore, Ki-67 was strongly expressed in 20% of tumor cell nuclei in our MTSCC case, which is unusual in these tumors. There were no reported cases of high Ki-67 proliferative activity in the previously reported MTSCC cases.

Simultaneous occurrence of lung cancer and renal mass usually happens in the setting of tumor metastasis. However, separate primary renal cell carcinoma can occur. Failure of the metastatic tumor to respond to therapy that is effective in the primary tumor raises the possibility that the presumed metastasis may actually represent a second primary tumor, as occurred in our case. Therefore, careful histologic evaluation is required to determine the nature of the presumed metastatic tumor. To the best of our knowledge, this is the first reported case of lung adenocarcinoma and MTSCC of the kidney occurring simultaneously in the same patient.

According to the diagnostic criteria by Warren & Gates, a double cancer is classified as a synchronous type or a metachronous type. Since the MTSCC was found less than 1 year after lung cancer had been found, our double cancer could be classified as a synchronous type. But, there are few reports of double cancer involving MTSCC, and few studies have reported the treatment and 5-year disease survival rate of patients with multiple primary malignancies of different histologic types, as observed in our case. However, it is believed that the neoplasm with the lowest 5-year disease survival rate should be treated first in cases of multiple primary malignancies of different histologic types, because it has the greatest potential to shorten the patient’s life. In our case, the lung cancer had to be treated first because of its lower 5-year disease survival rate, although high positivity of Ki-67 and p53 was observed in MTSCC.

In summary, we report one case of MTSCC with regional lymph node metastasis, occurring in a lung cancer patient. According to our review of the literature, this is the first case report involving a concurrent MTSCC of the kidney and pulmonary adenocarcinoma. The kidney tumor revealed neuroendocrine differentiation as well as p53 and Ki-67 overexpression. Expression of p53 staining and Ki-67 overexpression may correlate with aggressive behavior and may be related to the lymph node metastasis seen in this case. However, to determine the true significance of p53 and Ki-67 overexpression in MTSCC, additional studies with long-term follow-up will be needed.

REFERENCES

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